DOCUMENTATION, ANTI-AGING ACTIVITIES AND PHYTOCHEMICAL PROFILING OF SELECTED MEDICINAL PLANTS USED BY JAKUN WOMEN IN KAMPUNG PETA, MERSING, JOHOR

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DEDICATION

For my *abah* (En. Ismail Bin Ebrahim) and *mama* (Pn Siti Habsah Bt. Hashim),
who always inspired me with their hardwork and successs,
who always love, pray and give endless support to their children.

And also for my lovely siblings (Izzati, Nabila & Amir) for their constant motivation and support along this journey.

May Allah reward them with Jannah

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ABSTRACT

Traditional knowledge of indigenous people could become the baseline information for the discovery of anti-aging agent. The objectives of this study were to document the knowledge of Jakun people in Kampung Peta, Mersing, Johor on medicinal plants for women's healthcare; to investigate the optimal formulations of herbal mixture used by Jakun women based on phytochemicals content and antioxidant activity; to determine the anti-aging potential of the selected formulations; and to investigate the major phytochemical constituents in the formulations. Based on qualitative analysis from semi-structured interview, twelve species of medicinal plants have been documented for women's healthcare. Among species documented, four species, *Cnestis palala* (Pengesep), *Urceola micrantha* (Serapat), *Labisia pumila* (Kacip fatimah) and *Microporus xanthopus* (Kulat kelentit kering) that were prepared in the form of mixture have been used for formulation study. About 24 formulations have been developed from the simplex centroid design and tested for total phenolic content (Folin-Ciocalteu method), total flavonoid content (aluminium chloride colorimetric method) and three different antioxidant assays (DPPH scavenging, ABTS decolourization and FRAP assays). Single formulation of *Cnestis palala*, single formulation of *Urceola micrantha* and binary mixture of *C. palala* and *U. micrantha* are among the optimal formulations with high phytochemicals content and antioxidant activities that were further evaluated for anti-aging activities. For anti-aging activities, five enzymatic assays have been tested on the three formulations which are matrix metalloproteinase-1 (MMP-1) inhibition, elastase inhibition, tyrosinase inhibition, acetyl- and butyrylcholinesterase inhibition assays. Single formulation of *U. micrantha* showed the highest inhibition towards MMP-1 (49.44 ± 4.11 %) and elastase enzymes (20.33±2.52%), while single formulation of *C. palala* showed highest inhibitions towards tyrosinase (14.06±0.31%), acetylcholinesterase (32.92±2.13%) and butyrylcholinesterase (34.89±2.84%) enzymes. The identification of phytochemicals compound have been carried out using gas chromatography-mass spectrometer (GC-MS), which showed the presence of 2,2-dimethoxybutane and 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP) in the three formulations extract. The presence of catechol and quinic acid in *U. micrantha* extract might possibly contribute to anti-aging activities of the extract. These findings could become baseline for the exploration of novel anti-aging agents from natural source by using the traditional knowledge of indigenous people.

ABSTRAK

Pengetahuan tradisi orang asli boleh menjadi maklumat asas kepada penemuan agen anti-penuaan. Objektif kajian ini adalah untuk mendokumenkan pengetahuan orang Jakun di Kampung Peta, Mersing, Johor terhadap tumbuhan ubatan yang digunakan untuk penjagaan kesihatan wanita; untuk mengkaji formulasi optimum bagi campuran herba yang digunakan oleh wanita Jakun berdasarkan kandungan fitokimia dan aktiviti antioksida; untuk menentukan potensi anti-penuaan bagi formulasi terpilih; dan untuk mengkaji komposisi fitokimia dalam formulasi. Berdasarkan analisis kualitatif dari temu bual separa berstruktur, dua belas spesies tumbuhan ubatan telah didokumenkan bagi penjagaan kesihatan wanita. Dari spesies yang telah didokumenkan, empat spesies, *Cnestis palala* (Pengesep), *Urceola micrantha* (Serapat), *Labisia pumila* (Kacip Fatimah) dan *Microporus xanthopus* (Kulat kelentit kering) yang di sediakan dalam bentuk campuran digunakan bagi kajian formulasi. Sekitar 24 formulasi telah dibangunkan menggunakan reka bentuk simpleks sentroid dan diuji untuk jumlah kandungan fenolik (kaedah Folin-Ciocalteu), jumlah kandungan flavonoid (kaedah kolorimetrik aluminium klorida) dan tiga asai antioksida (asai penghapusan DPPH, penyahwarnaan ABTS dan FRAP). Formulasi tunggal *Cnestis palala*, formulasi tunggal *Urceola micrantha* dan campuran perduaan *C. palala* dan *U. micrantha* adalah antara formulasi optimal dengan kandungan fitokimia dan aktiviti antioksida yang tinggi, yang dinilai bagi aktiviti anti-penuaan. Bagi aktiviti anti-penuaan, lima asai enzim telah diuji bagi tiga formulasi, iaitu asai perencatan matriks metalloproteinase-1 (MMP-1), perencatan elastase, perencatan tirosinase, perencatan asetil- dan butirilkolinesterase. Formulasi tunggal *U. micrantha* menunjukkan perencatan yang tinggi terhadap MMP-1 (49.44 ± 4.11 %) dan enzim elastase (20.33±2.52% perencatan), mankala formulasi tunggal *C. palala* menunjukkan perencatan yang tinggi terhadap enzim-enzim tirosinase (14.06±0.31%), asetilkolinesterase (32.92±2.13%) dan butirilkolinesterase (34.89±2.84%). Pengenalpastian sebatian fitokimia telah dijalankan menggunakan kromatografi gas-spektrometri jisim menunjukkan kehadiran 2,2-dimetoksibutane and 2,3-dihidro-3,5-dihidroksi-6-metil-4H-pyran-4-one (DDMD) di dalam tiga ekstrak formulasi. Kehadiran katekol dan asid kuinik dalam ekstrak *U. micrantha* berkemungkinan dapat menyumbang aktiviti anti-penuaan bagi ekstrak. Penemuan ini dapat menjadi asas kepada penerokaan agen anti-penuaan yang baharu dari sumber semulajadi dengan menggunakan pengetahuan tradisi orang asli.

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LIST OF SYMBOLS AND ABBREVIATION

˚C	-	Celsius
h	-	Hour
L	-	Liter
mL	-	Milliliter
mg	-	Milligram
min	-	Minute
µL	-	Microliter
µM	-	Micromolar
µU	-	Microunit
nm	-	Nanometer
R^2	-	Coefficient of determination
Aβ	-	Amyloid Beta
ABS	-	Access and benefit sharing
ABTS		2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulphonic acid
AChE	-	Acetylcholinesterase enzyme
AD	-	Alzheimer's Disease
AP-1	-	Activator protein-1
BuChE	-	Butyrylcholinesterase enzyme
$CaCl_2$	-	Calcium chloride
CBD	-	Convention on Biological Diversity
CE	-	Catechin equivalent
DMSO	-	Dimethylsulfoxide
DNA	-	Deoxyribonucleic acid
DOE	-	Design of Experiment
DDMP	-	2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one
DPPH	-	2,2-diphenyl-1-picrylhydrazyl
DTNB	-	5,5'-dithio-bis-[2-nitrobenzoic acid]
ECM	-	Extracellular matrix

FDA	-	Food and Drug Administration
FRAP	-	Ferric-reducing antioxidant power
GAE	-	Gallic acid equivalent
GC-MS	-	Gas Chromatography- Mass Spectrometry
HEPES	-	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
IK	-	Indigenous knowledge
JAKOA	-	Department of Orang Asli Development
L-DOPA	-	L-dihydroxyphenylalanine
MAPK	-	Mitogen-activated protein kinase
MMP	-	Matrix metalloproteinase
MRNA	-	Messenger ribonucleic acid
NNGH		N-Isobutyl-N-(4-methoxyphenylsulfonyl) glycylhydroxamic
PIC	-	Prior Informed Consent
PTNJ	-	Johor National Park Corporation
ROS	-	Reactive oxygen species
TBARS	-	Thiobarbituric acid reactive substance
TEAC	-	Trolox equivalent antioxidant capacity
TFC	-	Total flavonoid content
TK	-	Traditional Knowledge
TMK	-	Traditional Medicinal Knowledge
TNJER	-	Taman Negara Johor Endau Rompin
TPC	-	Total phenolic content
TPTZ	-	2,4,6-tripyridyl-S-triazine
TRP-1	-	Tyrosinase related protein 1
UV	-	Ultra violet
VMS	-	Volatile methylsiloxane
WHO	-	World Health Organization

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LIST OF PUBLICATIONS

Journals :

i. **Ismail, N. A.,** Abu Bakar, M. F., Kormin, F., Linatoc, A. C., Maryati, M. 2017. Application of statistically mixture simplex-centroid design to optimize the TPC and TFC on the proportion of polyherbal formulation used by Jakun women. *Journal of Engineering & Applied Science* (SCOPUS). [Accepted].

ii. **Ismail, N. A**., Abu Bakar, M. F., Kormin, F., Maryati, M., Akim, A., Isha, A. Anti-aging potential and phytochemical screening of optimal formulations from selected medicinal plants used by Jakun women in Kg. Peta, Johor. *Oxidative Medicine and Cellular Longevity* (SCOPUS). [Submitted]

Proceedings/ Conference/Seminars :

i. **Ismail, N. A**., Maryati, M. & Abu Bakar, M. F. (2015). Medicinal Plants Used For Women's Healthcare Among The Jakun Community In Kg. Peta : A Preliminary Study. In O. Asiah, H. Lim, B. Chee, M. N. Musaadah, M. Mastura, K. Getha, S. Vimala (Eds.), *Proceeding FRIM No. 7* Persidangan Industri Herba (pp. 303–308). Putrajaya: Forest Research Institute Malaysia

CHAPTER 1

INTRODUCTION

1.1 Background of study

Aging is inevitable and considered as natural biological process. However, the changes in physiology of human due to aging are undesirable. Aging is physiologically characterized as a continuous, generalized systemic organ dysfunction, which lead to the increased vulnerability to environmental challenge and increase the tendency to suffer diseases and death. Generally, the incidence of degenerative diseases such as osteoporosis, cardiovascular disease, type 2 diabetes, cancer and Alzheimer's disease escalated with increasing age (Si & Liu, 2014) .

Physically, the obvious sign of aging could be seen on the skin with the formation of wrinkles and atypical pigmentation (Masaki, 2010). The skin condition such as epidermal thinning, reduction in dermal collagen content, decreased in laxity diminished skin moisture, and impaired wound healing have been reported in post-menopausal women (Irrera *et al*., 2017). Exposure of skin to extrinsic factors (environmental aggressor such as UV radiation and smoking) is in the 4^{th} rank that contribute to the nonfatal disease burden and the effects arise as humans get older (Tobin, 2017).

Brain also would be affected as person aged. Normal aging will cause decline in brain function and increase the tendency to suffer from neuronal degeneration. The decline in brain cholinergic system, that contribute to memory function will eventually lead to various age-related neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease (AD), multiple sclerosis, Huntington disease and amyotrophic lateral sclerosis (Solanki *et al*., 2016). Other than individual genetic factors, the external factors such as nutrition, smoking, alcohol,

environmental conditions could contribute to the aging in human. Oxidative stress has been identified to be one of the major factors that accelerates the aging process (Rahal *et al*., 2014). Oxidation will cause oxidative injury to the neuron and skin structure. Antioxidant compounds are able to defend human body from oxidation process. Eventhough human body contains its own self defense system, it is insufficient to fight against the cumulative damage due to reactive oxygen species (ROS).

Plants are known to contain numerous bioactive compounds which could potentially act as antioxidant with anti-wrinkle and anti-Alzheimer's properties that protect the skin against key enzyme in wrinkle formation and brain from aging (Nema *et al*., 2011). The exploration of medicinal plants as potential for anti-aging supplement or drugs are rapidly growing for the past few years. According to Global Industry Analyst, nutricosmetic market is estimated to reach US$ 7.4 bilion by 2020, driven by "beauty from within" trend (Analyst, 2015). This indicates that people worldwide are constantly searching for the intervention with nutraceutical benefit that could lead to the improvement and maintenance of their appearances and internal health. The nutricosmetic is the result of convergence between nutraceutical and cosmaceutical field with major claim as an anti-aging (Anunciato & Filho, 2012). The examples of nutricosmetic products include "beauty pills", tablets, liquid (i.e herbal tea), granulates or foods formulation which is believe to be able to reduce wrinkle formation by fighting free radicals generated by solar radiation (Taeymans *et al*., 2014).

More than 89 medicinal plants have been used for cosmetic applications in Malaysia, such as *Centella asiatica* (Apiaceae), *Cosmos caudatus* (Asteraceae), *Curcuma xanthorrhiza* (Zingiberaceae) and *Ficus deltoidea* (Moraceae) are traditionally known to preserve youthful appearance of women (Narayanaswamy & Ismail, 2015). Usually, these plants contain antioxidant with anti-wrinkle properties. In spite of the wrinkle inhibition, the antioxidant also possess cholinesterase inhibitory activities which is one of the treatment in AD prevention. In a review by Natarajan *et al*. (2013) on Asian plants, more than 40 herbal remedies have been used traditionally and being proven scientifically to possess anti-inflammatory, anti-cholinesterase andantioxidant activities, which are contributed by its bioactive compounds such as alkaloids, flavonoids, steroids, saponins, terpenoids and essential oils. Despite the progress made in aging and Alzheimer's disease research in the last

decades, no treatment with a strong disease-modifying effect is currently available (Natarajan *et al*., 2013).

Traditional knowledge (TK) on medicinal plants has been one of the sources in drug discovery from natural sources. TK has been defined as the knowledge, innovations and practices of indigenous and local communities around the world which were developed from experience gained over the centuries and adapted to local culture and environment, and transmitted orally from generation to generation (MoNRE, 2012). Traditional Medicinal Knowledge (TMK) is one of the sub categories of TK, other than traditional agricultural and ecological knowledge (Van Overwalle, 2005). According to World Health Organization (WHO, 2003), about 80% of people around the world utilize traditional medicine as their primary healthcare whereas 65% of citizen in developing nation use traditional medicine as an alternative to their healthcare maintenance. In National Policy on Biological Diversity 2016-2025, TK has been highlighted to be one of the key elements in conservation and sustainable uses of biodiversity (MoNRE, 2012). In addition, Malaysia has implemented an act on Access to Biological Resources and Benefit sharing bill 2017 in order to preserve the traditional knowledge of local and indigenous people, and also to ensure the fair and equitable sharing from the knowledge provided by the indigenous people.

Malaysia is ranked 12th among countries of the world with megabiodiversity and at least 95 subgroups of indigenous people that make up Malaysia's multiracial population (Masron *et al*., 2013). The wonderful knowledge and respect towards plants have originated from indigenous people, usually called 'Orang Asli', who inherited the knowledge and practices from their ancestors (Adnan & Othman, 2012). The indigenous and local communities usually live in an area where majority of plants genetic resources are found. In this regard, the preservation of the TK through documentation is crucial to maintain the biodiversity in Malaysia (MonRE, 2012). However, TK suffer from erosion and biopiracy. These documentation is the utmost defensive approach for conserving the TK from erosion, acquisition and exploitation by third parties (Van Overwalle, 2005).

Jakun, Orang Kuala, Orang Kanaq, Orang Seletar and Temuan are ethnic groups recognized as orang asli that live in the southern part of Malaysia, Johor (Masron *et al*., 2013). The Jakun tribe, who live in Kampung Peta, Endau, Mersing, Johor are the holder and users of TK. Despite modernization of this country, most of

the older generations in Jakun community still rely on traditional medicine for their healthcare. They utilize plants and animals to treat various ailments. The earliest record of ethnomedicinal knowledge of Jakun on plants has been documented by Taylor & Wong (1987), whereas the recent documentation of plant by Jin (2005) include the use of palm for medicinal purposes, Ismail *et al*. (2015) on the medicinal plants used for malarial treatment and Sabran *et al.* (2016) on medicinal plants used for treatment of tuberculosis. However, no study has been focusing on the use of medicinal plants specifically for maintenance of women's healthcare in Jakun community. The Convention on Biological Diversity (CBD) has recognized the role of women and local communities in conservation of biological diversity. In fact, a review on medicinal plants used for women healthcare in South-East Asia revealed 2000 different plant species have been used in 5000 combinations to treat various ailments for women (Boer & Cotingting, 2014). There is a clear need to document the TK of women in Jakun community on the use of medicinal plants, particularly in health and beauty maintenance.

While taking into account the individual medicinal plants for the treatment of disease, the consumption of traditional herbs in the form of mixture is believed to exert higher pharmacological and therapeutic efficacy compared to the single medicinal plants (Guimarães *et al.*, 2011; Wang *et al*., 2014). Few reported studies showed that mixture of medicinal plants exhibit higher bioactivities compared to the single plants (Xu *et al*., 2014). The mixture is said to be able to increase the medicinal properties of individual species, reduce toxicity and improve the taste acceptance (Guimaraes *et al*., 2013). In traditional chinese medicine (TCM), some of the anti-dementia herbal formulation have been proved scientifically to exert dementia inhibition effect (Kong *et al.*, 2009). The different herbs exert different effects and when combined, it acts either in synergistic, antagonistic or additive manner. The knowledge regarding the herbal mixture have been passed from older generation to the current generation of herbal practitioner and skillfull healer. Traditionally, the herbal plants that was prepared as mixture have similar therapeutic effects and benefits with possible of synergistic effects (Boer & Cotingting, 2014; Guimaraes *et al*., 2013). Based on the documentation by Taylor & Wong (1987) in Jakun community, some ailments could be treated by mixture of medicinal plants. Thus, the documentation of medicinal plants for women's healthcare maintenance

and investigation on the herbal mixture used by Jakun women for anti-aging might provide the baseline data for the exploration of anti-aging treatment.

1.2 Problem statement

Aging has been associated with undesirable effects towards physiology and psychology of a person. Although many treatments have been applied to cure or delay these pathologies, it have been found to be ineffective or associated with side effects. Nutricosmetic product with anti-aging claim has increased its popularity in the market, eventhough the efficacy of this product has not been proven scientifically (Draelos, 2010).

Furthermore, the prevalence of neurodegenerative diseases also increase yearly. According to Alzheimer's Disease Foundation Malaysia (ADFM), currently, it is estimated that 50,000 Malaysians suffer from Alzheimer's disease. The incidence of AD could double every five years beyond the age of 65. Although some of the drugs been approved by United State Food and Drug Administration (FDA) for the treatment of AD (i.e Donepezil, Galantamine, Rivastigmine, and Huperzine A), the outcomes are often unsatisfactory (Natarajan *et al*., 2013; Association, 2014) and associated with side effects such as headache, diarrhoea, drowsiness and vomiting among others.

With regards to the mentioned problems, there is a great demand to develop a safe and more effective cure for skin and brain aging, and medicine to cure and treat these undesirable conditions. Traditional knowledge which is one of the resources in drug discovery is vulnerable to multiple factors, such as erosion and modernization (WIPO, 2001). Thus, the documentation of TK and the investigation on the bioactivities of selected plants might preserve the knowledge and validate the traditional claim.

1.3 Objectives

This study aimed to integrate the traditional knowledge of indigenous people for women health maintenance and to investigate scientifically the potential of the medicinal plants for anti-aging. This aim could be achieved through following specific objectives:

i. To document the knowledge of Jakun people on medicinal plants for women healthcare.

ii. To determine the optimal formulations of selected herbal mixture used by Jakun women based on phytochemicals content and antioxidant activities.

iii. To determine the anti-wrinkle (elastase and collagenase inhibition activities) and anti-hyperpigmentation (tyrosinase inhibition activity) of optimal formulations.

iv. To determine the anti-Alzheimer potential (acetylcholinesterase inhibition and butyrylcholinesterase inhibition activities) of optimal formulations.

v. To profile the phytochemical constituents of the selected plants extracts that potentially contributed to the anti-aging properties of optimal formulations.

1.4 Significance of study

In recent years, increasing attention has been paid in searching for solution to reduce the effect of aging. While most of the products with anti-aging claim contain synthetic chemicals which harmful to human, medicinal plants with diverse phytochemicals has been shown to be a better solution as anti-aging agent (Kapoor, Dureja, & Chadha, 2009a). Findings from this study provide scientific evidence on the potential of medicinal plants as anti-aging agent by employing the traditional knowledge of Jakun people on medicinal plants. Besides that, this finding also provides the evidence on the synergistic effects of herbal mixture that is usually believed to be able to exert more therapeutic effects (Guimaraes *et al*., 2011) as compared to the single herbs. Thus, the evidence of this study will be useful in selecting the formulations with more health benefits and anti-aging effects.

CHAPTER 2

LITERATURE REVIEW

2.1 Documentation of traditional knowledge

2.1.1 Definition of terms

The Convention on Biological Diversity (CBD) in Article 8 (j) has described the term traditional knowledge as :

> …. the knowledge, innovations and practices of indigenous and local communities around the world, developed from experience gained over the centuries and adapted to the local culture and environment, and transmitted orally from generation to generation. It tends to be collectively owned and takes several forms from stories, songs, folklore, proverbs, cultural values, beliefs, rituals, community laws, local language and agricultural practices, including the development of plant species and animal breeds. (MoNRE, 2012)

The term "traditional" does not refer to "old", but it is rather the traditions that have been passed from generations to generations. It relates to the way the knowledge has been created, preserved and disseminated (Finetti, 2011). Traditional Knowledge (TK) comprise of tangible and non-tangible elements (WIPO, 2012). The tangible element of TK is the genetic resources, while the intangible element is the knowledge. The TK sometimes refers as indigenous knowledge (IK). The IK is actually a subset of TK, where the users are communities, people and nation that are indigenous (Van Overwalle, 2005) and the knowledge is only known by the specific community (Finetti, 2011). The traditional knowledge could be further classified into three categories, which are traditional medicinal, agricultural and ecological knowledge (Van Overwalle, 2005). Traditional medicine is defined as the compilation of knowledge, skills and practices based on theories, belief and

experiences native to different cultures, where understandable or not, used for health maintenance as well as in the prevention, diagnosis, improvement or treatment of mental and physical illness (WHO, 2000)

Documentation of TK is defined as a process of identifying, collecting, organizing, registering or recording TK, in order to maintain, manage, use, disseminate and/or protect TK according to specific aims. This knowledge is not limited to simple photographing, or isolated record of tradition, or written notes, but the isolated act need to undergo comprehensive, thought-through process to be regarded as 'documentation'. The most significant thing that needs to be considered while documenting TK is consultation (with and among indigenous or local people), participation and prior informed consent (PIC) before the documenting process starts (WIPO, 2012).

The traditional medicine usually involves all organisms such as animals, plants, and microbes in the treatment of illness by local or indigenous people. Another term that is usually being used in traditional knowledge field is ethnobotany. Ethnobotany and ethnopharmacology are interdisciplinary field that focused on empirical knowledge of indigenous people regarding medicinal substances, their potential health benefits and side effect associated with such remedies (Gurib-fakim, 2006). Ethnobotany has not only restricted to plants, but also involves the studies of algae, lichens and fungi (Eldeen *et al*., 2016). In the current study, the utilization of medicinal plants, including fungi were investigated among Jakun women in Kampung Peta.

2.1.2 The importance of documenting the traditional knowledge

2.1.2.1 Conserving genetic resources and natural heritage

The traditional knowledge on the uses of organisms including animals in traditional medical system, is important to be documented as the biodiversity is eroding from day to day (Alves & Rosa, 2007). Destructive exploitation of the tropical forest such as illegal logging and conversion of forest to plantation have become the key to the loss of biodiversity and global climate. The precious medicinal plants which have the potential to be developed as useful drugs might be lost along with the forest degradation. In Malaysia, the TK documentation is increasing. Likewise, Forest Research Institute Malaysia (FRIM) with other organizations and universities are

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